DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

October 30, 1996

Our Reference Nos: 95-1142 & 95-1167

Karl-Heinz Sellinger, Ph.D.
Boehringer Mannheim GmbH
Werk Penzberg
Nonnenwald 2
82377 Penzberg
Federal Republic of Germany

Dear Dr. Sellinger:

This letter hereby issues Department of Health and Human Services Biologics License No. 1211, to Boehringer Mannheim GmbH, Penzberg, Federal Republic of Germany, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture and import into this country for sale, barter, or exchange, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture and ship the product Reteplase. Reteplase is indicated for use in the management of acute myocardial infarction (AMI) in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI.

Under this authorization, you are approved to manufacture Reteplase drug substance at your facility in Penzberg, Germany. Final Reteplase drug product will be formulated, filled, lyophilized and labeled at your facility in Mannheim, Germany. Reteplase will be packaged into a kit with components for reconstitution and the kit labeled by [redacted] (b)(4). Nonbiological kit components will be supplied by contract suppliers as specified in your license application. Reteplase will be distributed by Boehringer Mannheim Corporation, Therapeutics Division, Gaithersburg, Maryland, under the trade name Retavase™. Boehringer Mannheim Corporation, Therapeutics Division, will also act on your behalf to receive adverse experience reports.

You are not currently required to submit samples of future lots of Reteplase to the Center for Biologics Evaluation and Research (CBER) for release under 21 CFR 610.2 by the Director, CBER. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for the dosage formulation of Reteplase shall be 24 months from the date of manufacture when stored at 2-25°C. The date of manufacture shall be defined as the date of the first sterile filtration of final formulated bulk. The dating period for the kit shall be 24 months or less, dependent upon the shortest expiration date of any component in the kit, when stored at 2-25°C. The drug substance may be stored for up to 24 months at -70°C. Results of ongoing stability studies should be submitted throughout the dating period as they become available, including the results of stability studies from the first three production lots.

We acknowledge your written commitments of April 3, 1996, May 30, 1996, July 2, 1996, July 10, 1996, October 21, 1996, October 25, 1996 and October 28, 1996 which include the following:

1. To submit results from additional studies on: two batches each of the end of production cells and crude inclusion bodies; drug product exposed to temperature fluctuations; reconstituted drug product at the end of the dating period; and the yellow discoloration in drug lyophilisate.

2. To further study and evaluate particulate formation in the drug product, including assessment of size distribution and in-process holding times, implement reference standards for the visual particulate inspection assay, and revise release specifications for particulates based upon commercial manufacturing experience.

3. To submit: the initial challenge test data for the HEPA filters at the Penzberg facility; the standard operating procedures for shipping and results of the shipping qualification studies; and standard operating procedures related to operating and testing of the in-line, 0.2 micron filters used in the compressed gas systems.

4. To submit a galley proof of the package insert for review and approval prior to implementation.

Any changes in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). These requirements became effective on December 27, 1994. All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed biologics license to the Director, Division of Application Review and Policy (HFM-585), Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Jerome A. Donlon, M.D.,Ph.D.
Director
Office of Establishment Licensing
and Product Surveillance
Center for Biologics
Evaluation and Research

Enclosure